REMARKS/ARGUMENTS

I. Status of the Claims

Claims ~~1-9, 11,~~ 19-24, ~~52-55, 57, 59-65,~~ 68-75, ~~77, 79-88, 90-99, and 101-103~~ are pending. Claims 8, 10, 12-18, 25-51, 56, 58, 66, 67, 76, 78, 89, 98, and 100 have been canceled. Claims 19-24, 59-65, 79-88, 90-97, 99, and 101-103 have been withdrawn from examination.

II. The Amendments Herein

The amendments herein add no new matter.

The claims reciting SEQ ID NO.:1 have been amended to recite that the 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2. The recitation is supported throughout the specification, including page 22, line 32, to page 23, line 4, Figure 1, and SEQ ID NO.:2.

The claims reciting that the toxin is a modified *Pseudomonas* exotoxin have been amended to clarify that the modified toxin is *Pseudomonas* exotoxin **A**, as supported by, for example, page 17, line 2.

III. The Office Action

The Final Office Action (hereafter, the "Action") rejects the claims on various grounds. Applicants amend in part and traverse the rejections. For the Examiner's convenience, the rejections are largely addressed below in the order in which they are presented in the Action.

A. Priority

The Action states that the underlying PCT application and the provisional application do not provide adequate support for one or more claims because the sequence of SEQ ID NO.:1 differs from those disclosed in the prior-filed applications. Action, at page 3.

It appears that the discrepancy in the sequence of SEQ ID NO.:1 as set forth in the provisional application and the PCT application is a single amino acid residue. Further

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A. Priority

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It appears that the discrepancy in the sequence of SEQ ID NO.:1 as set forth in the provisional application and the PCT application is a single amino acid residue. Further examination indicated that the difference is due to a mistranslation of a codon in the nucleic acid sequence set forth in the provisional application and the PCT application as SEQ ID NO.:2. As the Examiner is no doubt aware, sequences for proteins are now usually determined by sequencing the nucleic acid encoding the protein and translating the sequence to obtain the amino acid sequence. Since the sequence set forth as SEQ ID NO.:1 in the priority applications does not reflect the correct translation of the nucleic acid sequence set forth in SEQ ID NO.:2, persons of skill in the art would immediately understand the sequence of SEQ ID NO.:2 to be the one representing the one actually sequenced and would immediately understand the correct amino acid sequence of the encoded peptide.

Notwithstanding the above, to expedite prosecution the claims have been amended to recite that the immunotoxins have the binding affinity of 3B3 Fv region consisting of a VH chain and a VL chains as encoded by SEQ ID NO.:2. The Action does not allege that SEQ ID NO.:2 is not entitled to claim priority from the underlying provisional and PCT applications.

B. Rejection of the claims as obvious

The Action maintains the rejection of the claims as obvious under 35 U.S.C. § 103(a) over Matsushita et al., Aids Research Human Retroviruses 6(2):193-203 (1990) (hereafter, "Matsushita"), in view of Barbas, PNAS 91:3809-3813 (1994) and Pastan, U.S. Patent No. 5,458,878. Applicants traverse.

The Action rejects the Applicants' assertions that any motivation provided by Matsushita to create env-targeted immunotoxins was extinguished by the failure of such a toxin in clinical trials, as reported by Ramchandran et al., J. Infect Dis 170:1009-13 (1994) ("Ramachandran") and by Davey et al., J. Infect Dis 170:1180-8 (1994) ("Davey"). According to the Action, the CD4-PE immunotoxins of Ramchandran and of Davey are not analogous to the instant invention "since they target different cellular components." Action, at page 6. For the Examiner's convenience, the various statements made by the Action in support of the rejection, and Applicants' responses thereto, are set forth below.

Accompanying this Amendment is a Declaration of Dr. David J. FitzGerald (the "Declaration"). Dr. FitzGerald has worked in the field of targeting toxins to cells since 1982. Declaration, at ¶ 5. He is specifically knowledgeable about the attempts to develop targeted toxins of CD4-*Pseudomonas* exotoxin A ("PE") for use as therapeutic agents for HIV-1 infection, as reflected by the fact that he was a co-author on the first study on the use of a CD4-PE chimeric toxin to kill HIV-1 infected cells, Chaudhary, V.K., Mizukami, T., Fuerst, T.R., **FitzGerald, D.J.**, Moss, B., Pastan, I., and Berger, E.A., "Selective killing of HIV-infected cells by recombinant human CD4-*Pseudomonas* exotoxin hybrid protein." Nature 335:369-372 (1988). (A copy of the abstract of this publication is attached as Attachment 2 to Dr. FitzGerald's Declaration.) Declaration, at ¶ 6. His work on the pre-clinical development of CD4-PE toxin conjugates as a therapeutic to treat HIV-1 disease is further reflected by his co-authorship on six additional publications on this subject, which are set out specifically in the Declaration at ¶ 7. The abstracts for three of these publications are available on PubMed and are provided as attachments to the Declaration.

Dr. FitzGerald is also familiar anti-gp120 antibody known as 3B3, as described in the specification of the captioned application, as well as the binding specificity and affinity of the Fv portion of this antibody and of the results of using immunotoxins composed of fusing the Fv portion of 3B3 (hereafter referred to as "3B3 Fv") to PE to kill cells infected with HIV-1. Declaration, at ¶9.

While the Examiner's attention is respectfully directed to the entirety of the Declaration, the Examiner's attention is respectfully directed specifically to the following.

1. The rejection is based on fundamental errors of fact regarding the cells bound by CD4-PE toxins of Ramachandran and Davey

On page 6, the Action states that the immunotoxins of Ramachandran and of Davey are not analogous to those of the present invention:

> " The immunotoxins of the instant invention . . . target cells expressing gp120 on their surface (i.e., infected cells) whereas the CD4-PE40 immunotoxin of Ramachandran et al. target any cell expressing CD4. Hence any 'results' based on the application of CD4-

> PE40 immunotoxin would not have any bearing on the perceived efficacy of immunotoxin based on the combination of the cited references. The same is true for the sCD[4]-PE immunotoxin disclosed by Davey et al."

Dr. FitzGerald states that the Action's position is factually incorrect and would have been known to be incorrect by a person of skill in the art as of the June 1998 filing date of the priority provisional application. Declaration, at ¶14. He states that CD4 is a cell surface marker on the surface of certain cell types, B cells and macrophages that is bound by the gp120 protein of HIV-1, and that CD4 does not bind to itself. *Id.* He further states that neither the CD4-PE40 immunotoxin of Ramachandran nor the sCD4-PE immunotoxin of Davey would bind cells expressing CD4, as stated by the Action. *Id.*

Dr. FitzGerald further states that the CD4-PE40 immunotoxin of Ramachandran and the CD4-PE immunotoxin of Davey were intended to bind were cells infected by HIV-1, which express gp120 on their surface and that the immunotoxins recited in the claims under examination have the binding affinity of the 3B3 Fv, which binds to the gp120 protein. Thus, he indicates that both (i) the CD4-PE40 immunotoxin of Ramachandran and the sCD4-PE immunotoxin of Davey, and (ii) the immunotoxins of the present invention, bind to cells expressing gp120, and not to cells expressing CD4. He states that he and others in the art would therefore consider them to be analogous in terms of the cells they were intended to bind. Declaration, at ¶ 15.

Dr. FitzGerald further notes that the Action states that

> "With regard to Point 4, contrary to Applicants assertion, CD4-P[E]40 immunotoxins would bind not only to cells expressing gp120, but also to any cell expressing CD4 on its surface."

Dr. FitzGerald states that the Action's statement is factually incorrect and would have been known to be incorrect by a person of skill in the art as of the June 1998 filing date of the priority application. Declaration, at ¶ 16. He states that, as already noted above, CD4 does not bind to itself, and that the Action is therefore incorrect in asserting that CD4-PE toxins bind "to any cell expressing CD4 on its surface." *Id.* Dr. FitzGerald states that CD4-PE toxins do bind (and kill) cells expressing gp120 on their surface, as reported in the publications listed in paragraphs 6 and

7 of his Declaration. And the only cells in the body that express gp120 are those infected with HIV-1. *Id.*

Dr. FitzGerald further notes that, on page 6, the Action states:

> "With regard to Point 5, since the CD4-PE40 immunotoxin would bind to any cell expressing CD4 on its surface, the hepatoxicity would logically be the result of said immunotoxin binding to healthy cells thereby disrupting some cellular or endocrine cascade present in man but not in the mouse."

Dr. FitzGerald states that this statement is factually incorrect and would have been known to be incorrect by a person of skill in the art as of the June 1998 filing date of the priority application. Declaration, at ¶ 17. First, he notes, again, that CD4 does not bind to itself, and that CD4-PE toxins therefore do not bind "to any cell expressing CD4 on its surface," as alleged by the Action. Declaration, at ¶17. Second, he states that cells in the liver (hepatocytes) do not express CD4. *Id.* Thus, he states that, even if the Action was not incorrect about CD4-PE binding to CD4, the Action's argument would fail to explain the hepatoxicity observed in the human trials of CD4-PE toxins. *Id.*

Accordingly, the rejection's contentions in response to Points 1, 2, 4, and 5 as set forth on pages 6-7 of the Action are grounded on clear errors of fact. The CD4-PE toxins of Ramachandran and Davey bind to the same cells as those targeted by the immunotoxins of the claims under examination. The conclusion of the rejection that the CD4-PE toxins of Ramachandran and Davey are not analogous to the immunotoxins of the claims under examination is therefore in error. The rejection should be reconsidered in light of the analogous nature of the toxins previously available in the art and, upon reconsideration, withdrawn.

2. The Action's factual errors also result in an incorrect analysis of the motivation of practitioners in the art

On page 7, the Action states:

> With regard to Point 6 [Applicants' argument that the Berger reference shows that, following the failure of the trials of the CD4-PE toxins of Ramachandran and Davey, enthusiasm for env-targeted immunotoxins was diminished], Applicants assertion

> that the failure of CD4-PE immunotoxins to live up to expectations . . . are deemed unpersuasive. . . . Moreover, the failure of a non-analogous immunotoxin, while it may have been discouraging would not necessarily remove the motivation provided by Matsushita, especially when his immunotoxin (which is analogous to the instant invention) was disclosed to have efficacy."

(Emphases added).

This ground for maintaining the obviousness rejection, like the ones set forth above, is based on the conclusion that the CD4-PE toxins of Ramachandran and Davey bind to a different target than those of the present invention, and therefore are not analogous. As shown in the preceding section, the Action's conclusion is based on the mistaken belief that CD4-PE toxins would bind to different cells than those bound by the immunotoxins recited in the claims under examination. The cells bound by the CD4-PE toxins of Ramachandran and Davey and those bound by the immunotoxins of the present claims are the same, and the CD4-PE toxins of the prior art and those of the instant claims are therefore analogous. See, FitzGerald Declaration at, e.g., ¶15.

While the rejection should be reconsidered for this reason alone, Applicants also note the following. In his Declaration, Dr. FitzGerald states that the CD4-targeted toxins, the 0.5β antibody of Matsushita, and the immunotoxins of the claims under examination all target cells expressing gp120, that is, HIV-1 infected cells. Declaration, at ¶19, item (i). He further notes that the antibody of Matsushita is specific for one type of HIV-1 and therefore binds only to cells infected by HIV-1 of the correct type, while both CD4 and the immunotoxins of the present invention would both bind to cells with less regard to the particular type of HIV-1 infecting the cells. *Id.* But, to the extent that they are considered as binding to HIV-1 infected cells in preference to cells that are not infected by HIV-1, they would be considered analogous by persons of skill in the art. *Id.*

Second, Dr. FitzGerald notes again that liver cells do not express CD4. Thus, even assuming that, contrary to fact, CD4-PE immunotoxins would bind to cells expressing CD4, there would be no reason to think that the hepatoxicity observed in trials of CD4-PE

immunotoxins would not also be found with respect to toxins targeted by the antibody of Matsushita. Id., at item (ii).

Third, Dr. FitzGerald considered the Action's comments that the antibody of Matsushita "was disclosed to have efficacy." Declaration, at ¶19, item (iii). The efficacy Matsushita discloses is that "toxin-conjugated anti-gp120 monoclonal antibody selectively killed HIV-infected cells in vitro." Matsushita, at page 199, second paragraph. Thus, the efficacy disclosed in Matsushita is similar to that disclosed in Dr. FitzGerald's publication in Nature two years earlier regarding the in vitro efficacy of CD4-PE in killing HIV-1 infected cells. See, Chaudhary et al., Nature 355:369-72 (1988). This would not by itself give persons of skill any reason to expect a different result with the 0.5β antibody of Matsushita than that found in clinical trials of CD4-PE toxins. Declaration, at ¶19, item (iii). Id.

Fourth, Dr. FitzGerald points out that Matsushita states that the 0.5β antibody is "type-specific." Matushiata, page 194, first line under heading "Antibody and immunotoxins." Matsushita notes in its discussion section that, while the binding activity of the 0.5β antibody was type specific, toxins conjugated to CD4 "also killed HIV-infected cells in vitro and were shown to be effective against [a] variety of divergent strains of HIV." Matsushita, at page 200, second paragraph. Thus, Matsushita itself indicated the superiority of CD4 as a targeting agent against HIV-1 infected cells to the antibody the Matsushita authors themselves had developed. Dr. FitzGerald avers that any motivation Matsushita provided to create anti-env immunotoxins was destroyed after the failure of the CD4 toxins that the Matsushita authors themselves indicated were more broadly applicable than those the immunotoxin they themselves had developed. Declaration, at ¶19, item (iv).

Fifth, Dr. FitzGerald states that both the immunotoxin of Matsushita and CD4-PE are toxins targeted to the envelope glycoprotein ("Env") of HIV-1, and states that, for all of these reasons, even assuming that Matsushita provided a motivation to make Env-targeted toxins prior to the of the CD4-PE trials, he disagrees with the Action's conclusion that Matsushita continued to provide such a motivation following the failure of those trials. Declaration, at ¶19, item (v).

In short, this portion of the rejection is based on the incorrect premise that the CD4-PE toxins of Ramachandran and Davey are not analogous to the immunotoxins under

examination while the Matsushita immunotoxin is. The rejection should be reconsidered in light of the discussion herein and, upon reconsideration, be withdrawn.

3. Matsushita did not "meet" the long felt need for AIDS treatments

The Action contends:

With regard to Point 7, the 'long felt need' for AIDS treatments was met by the teachings of Matsushita and would provide additional motivation for the skilled artisan to further refine the teachings of Matsushita.

Action, at page 7.

As noted above, Dr. FitzGerald is a co-author on seven publications on the development of CD4-targeted toxins for treatment of AIDS and is thus knowledgeable about the need for immunotoxins as therapeutics for AIDS. He disagrees with the contention that Matsushita's teachings "met" the "long felt need" for AIDS treatments. Dr. FitzGerald notes that Matsushita's 0.5β antibody-based immunotoxin is not only type-specific, but is also targeted to an epitope that even Matsushita admits is "within a highly variable region of gp120." Matsushita, at page 194, first full paragraph. See, Declaration, at ¶20. Indeed, the Matsushita antibody proved unsuitable for clinical development since the site it binds is one the HIV-1 virus readily mutates so that infected cells do not express the epitope bound by the antibody. *Id.* He is not aware today, some 16 years after the publication of Matsushita in 1990, that the Matsushita 0.5β antibody was ever brought into pre-clinical development. *Id.* It therefore clearly did not "meet the long-felt need" for an AIDS treatment, as asserted by the Action. In contrast, 3B3Fv-targeted immunotoxins of the claims are continuing to be successful in pre-clinical studies, including one designed to see if the immunotoxin would induce the same hepatoxicity as that seen in the CD4-PE trials referenced above. See, Kennedy et al., J Leukoc Biol (August 2006). A copy of the abstract of this publication is attached as Attachment 6 to the Declaration.

4. The Action's citation of the Goldstein reference for data presented after the priority date lends no support to the obviousness rejection

In a prior response, the Applicants pointed to Goldstein et al., J Infectious Diseases 181:921-6 (2000) ("Goldstein") for its retrospective statement as to what persons of skill thought following the publication of the Ramachandran and Davey references. This contention is now listed as point 3 of the Applicants' arguments, to which the Action states:

"With regard to Point 3, the Goldstein et al. reference discloses that Env-target toxins have therapeutic efficacy thus supporting the validity of the Matsushita reference." Action, at page 6. (While the Action is not clear in what it means by "supporting the validity of the Matsushita reference", presumably it intends to suggest that Goldstein supports the Action's contention that Matsushita met the long felt need for an AIDS treatment.)

Applicants respectfully note that Goldstein was cited by the Applicants for its statement that, in the wake of the Ramachandran and Davey reports, the approach of using anti-HIV antibodies as targeting moieties for anti-HIV immunotoxins was abandoned. This statement was fair to bring into this proceeding because the statement characterizes what people of skill in the art thought following the publication of those reports, and does not rely on data that was not available at the time the invention was made. The data that Goldstein presented in 2000 on the use of env-targeted toxins in combination of highly active antiretroviral therapy, or "HAART", on the other hand, was not available to the persons of skill in the art at the time the invention was made (that is, as of the 1998 priority date of the underlying provisional application) and therefore cannot represent information relevant to how a person of skill would have read Matsushita at the time the invention was made. The Action's attempt to use Goldstein to support its conclusions regarding the Matushita reference are therefore improper. And, of course, the Applicants have now presented competent evidence, in the form of a Declaration by a person of skill in the relevant field, that the Matsushita reference did not "meet" the long felt need for an AIDS therapeutic.

5. Conclusion regarding the obviousness rejection

MPEP §2144.08 III. instructs the Examining Corps that:

> A determination under 35 U.S.C. 103 should rest on all the evidence and should not be influenced by any earlier conclusion. *See, e.g., Piasecki*, 745 F.2d at 1472-73, 223 USPQ at 788; *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). Thus, once the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record. *See, e.g., Piasecki*, 745 F.2d at 1472, 223 USPQ at 788; *Eli Lilly*, 902 F.2d at 945, 14 USPQ2d at 1743.

In the instant case, the Applicants have presented rebuttal evidence in the FitzGerald Declaration, which shows that the obviousness rejection is grounded on a serious misunderstanding of the facts and a fundamentally flawed analysis of which prior art targeted toxins are analogous. Under MPEP §2144.08 III, the previous conclusion of obviousness must be reconsidered in light of all the evidence, including that submitted with this Amendment. Upon reconsideration, it should be withdrawn.

C. Rejection of the claims as indefinite

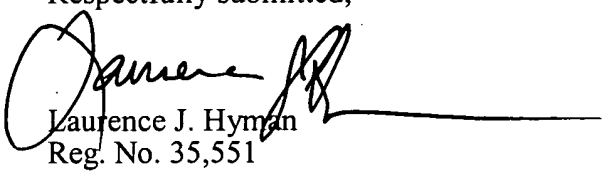
The Action rejects claims 1-7, 9, 11, 52-55, 57, 68-75, and 77 under §112, second paragraph as allegedly indefinite. According to the Action, the recitation of SEQ ID NO.:1 within parentheses in the independent claims renders them indefinite because it is, according to the Action, unclear whether the recitation is open or closed claim language. As noted above, the claims have been amended for other reasons to change the recitation within the parentheses. The amendment is believed to render this rejection moot.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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